Computerised Cognitive Training in Cognitively Healthy Older Adults: A Systematic Review and Component Network Meta-Analysis

Nathalie H. Launder, Amit Lampit

Department of Psychiatry, University of Melbourne

Abstract

Background: Computerised cognitive training (CCT) is common intervention that aims to enhance and maintain cognitive functioning with robust evidence for efficacy in older adults. Yet CCT corresponds to not one but an array of possible interventions that combine different components, and which combinations of components are most likely to be efficacious remains unknown. We therefore aimed to identify the cognitive benefits of CCT components and their combinations.

Methods: Using data from a recent systematic review of CCT in healthy older adults, we coded the components used in each intervention and control arm based on common theoretical frameworks of cognitive interventions. Comparisons of key intervention components and their combinations were conducted using component network meta-analysis models. The primary outcome was change from baseline to post-intervention in an overall cognitive composite for each component and combinations thereof versus passive control.

Results: Ninety-one studies encompassing 9,269 participants across 218 CCT and control arms were included. We found structured approaches to cognitive training to be more beneficial than unstructured cognitive activities or computer games, especially when training is adaptive. Efficacy appears to be even further enhanced when participants are also taught cognitive strategies. Intervention designs that included classical cognitive training, adaptivity, action video games and strategy training were associated with greater benefits, albeit precision was generally low.

Conclusions: Adaptive CCT may be beneficial for overall cognition in healthy older adults, particularly when combined with strategy training. Future work is required to identify interactions across components and the role of individual factors.

Introduction

As populations age cognitive decline and impairment are becoming increasingly costly health and social issues. Currently approximately 50 million people worldwide live with dementia, with global costs estimated at US$1 trillion annually – by 2050, this number is projected to increase to 152 million people.[1] However, there is growing evidence to support targeting potentially modifiable risk factors for the prevention or delay of dementia. The 2020 *Lancet* Dementia Commission estimated 40% of all cases of dementia can be accounted for by 12 potentially modifiable risk factors, many of which are thought to delay or prevent onset of dementia by maintaining a cognitively active lifestyle.[2] Thus, whilst cognitive decline is a normal aspect of aging, interventions that can support cognition in older adults and prevent or attenuate such decline towards mild cognitive impairment and dementia may have a substantial health and economic impact.[2,3]

Given strong links have been found between active participation in cognitively stimulating activities throughout the lifespan and compression of cognitive morbidity, enhanced late-life cognition, and reduced risk of cognitive impairment and dementia, there has been growing interest in cognitive interventions in recent years.[4-7] These interventions fall into three broad categories: cognitive stimulation, cognitive rehabilitation and cognitive training. Of key interest is cognitive training, defined as repeated practice on standardised cognitively demanding tasks that target specific cognitive processes.[8,9] Cognitive training is distinct from cognitive stimulation and cognitive remediation by its more structured focus on the formal training of cognitive abilities and processes.[10] Furthermore, based on promising evidence cognitive training has been highlighted as one of three priority areas for prevention research for cognitive decline and dementia in a review commissioned by the National Institute on Ageing.[11]

In particular, computerised cognitive training (CCT), a common type of cognitive training approach, has gained considerable attention as an intervention to maintain and enhance cognition in older adults. CCT delivers cognitive training using game-like interfaces and is especially appealing as it is inherently safe, can be adapted to individual needs and performance, provides ongoing feedback and can be delivered inexpensively at scale in both clinical and community settings.[9,10] To date, the efficacy of CCT in healthy older adults has been investigated in more than a dozen meta-analyses, with most reviews finding support for a benefit of CCT for cognition.[12] Within those, larger meta-analyses reported small-to-moderate heterogeneity (i.e., variance in effect sizes across studies), but found little evidence that such heterogeneity can be linked to risk of bias within (e.g., study quality, type of control) or between studies (mainly small-study effect).[13,14] Instead, previous reviews associated heterogeneity between studies to specific design factors such as dose, settings and broad intervention targets.[13,14]

Yet critically, CCT does not correspond to one specific treatment, but rather encompasses an array of modalities (treatment approaches distinguishable by their general methods or targets) comprising different components (elements or techniques that have the potential to casually influence the outcome of a modality). Reviews of CCT reveal considerable methodological heterogeneity, including modality design (e.g., home-based, supervised), different combinations of components within modalities (e.g., multidomain, adaptive training) and adjacent interventions (e.g., psychoeducation, physical exercise).[13-15] This variability has contributed to a lack of clarity regarding which CCT modalities may be beneficial for different outcomes, as well as scepticism towards CCT deriving from misleading marketing claims by 'brain-training' companies.[16] However, previous *pairwise* meta-analyses were unable to discern the various moderating elements beyond broad design factors, as studies that use a particular approach (e.g., supervised training) may differ in other important ways (e.g., dose, content). Therefore, the nature of CCT as a complex multicomponent intervention underscored the need to examine with greater precision which CCT components and modalities are critical for clinical benefits.

Network meta-analysis (NMA) can be used to compare multiple interventions for the same condition. NMA combines both direct evidence from trials that compare interventions head-to-head (e.g., A vs. B) and indirect evidence from common treatment comparisons in the rest of the network (e.g., using studies comparing A vs. C and studies comparing B vs. C to indirectly estimate A vs. B, see **Figure 1**).[17] NMA can be used to estimate relative effects for every treatment comparison in the network, regardless of whether or not treatments have been compared directly.[18-20] A previous *NMA* found that the efficacy of CCT varied widely across designs (e.g., supervision, dose) but found no evidence for a moderating effect of risk of bias or control type,[21] further indicating that observed differences in efficacy are likely due to differences in the CCT treatments.

Although NMAs may be more informative than pairwise meta-analyses for this purpose, they are still limited in their ability to account for complex multicomponent interventions such as CCT. As such, component NMA (cNMA) has been proposed as an extension of NMA.[22-27] Whereby cNMA allows for the dismantling of complex multicomponent interventions[28] into common components to identify their individual contributions to the effect of the combined intervention.

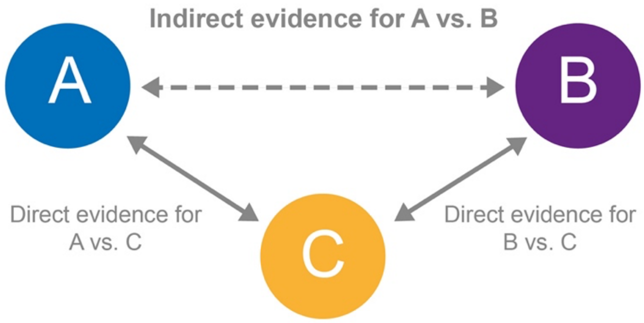

Figure 1. The effect size for the comparison *A* vs. *B* can be estimated indirectly using direct evidence from trials comparing *A* vs. *C* and *B* vs. *C* (adapted from Riley et al. BMJ 2017;358:j3932).

Whilst cNMA has been conducted in the past to investigate other complex multicomponent interventions that share similar challenges, such as cognitive behavioural therapy,[23,26] psychotherapy[22,27] and parenting interventions,[29] it is yet to be applied to CCT. We therefore aim to update and extend the findings of our previous systematic review and NMA of the field,[21] by conducting a cNMA of narrowly defined CCT in healthy older adults to investigate (1) the efficacy of individual CCT components, (2) identify the most effective combinations of components for improving cognitive outcomes and (3) to recommend theoretically optimal CCT modalities for future research and clinical practice.

Methods

This review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[30,31] Furthermore, as this review is an extension upon our previous NMA,[21] eligibility criteria and some of the data from our previous NMA were used.

Eligibility Criteria

We included RCTs investigating the effects of CCT compared to control conditions on one or more cognitive outcome(s) in cognitively healthy older adults (mean participant age ≥60 years). Studies that specifically targeted participants with major cognitive (including mild cognitive impairment), neurological, psychiatric and/or sensory impairments were excluded. CCT was defined as ≥4 h of practice on standardised computerised tasks or video games with clear cognitive rationale, administered on personal computers, mobile devices or gaming consoles. Eligible controls included passive (wait-list, no-contact) and active (e.g., sham CCT, alternative cognitive activities, psychoeducation) control groups. Studies combining CCT with other interventions (e.g., physical exercise) were eligible as long as both arms received the same adjacent interventions. When combined interventions were compared to passive control, studies were included only if CCT comprised ≥50% of the intervention time. Outcome measures that closely resembled one or more of the trained tasks were excluded.

Information Sources and Study Selection

MEDLINE, Embase and PsycINFO databases were searched through the OVID interface using the search terms "cognitive training OR brain training OR memory training OR attention training OR reasoning training OR computerized training OR computer training OR video game OR computer game". No restrictions on language or type of publication were applied. The first search was completed from inception to July 2014[14], and search updates were applied in November 2015, February 2018 and August 2019. In each update, two or more independent reviewers performed title and abstract screening as well as full-text screening, with disagreements at each stage resolved by consensus or by involvement of a senior reviewer. No further search update since August 2019 was applied for this review.

Data Extraction and Coding

Outcome data, extracted as mean and standard deviation (SD) for each group at each timepoint (baseline and immediately post-training) or measures of change (e.g., pre-post mean and SD of change within groups), and coding of CCT and control treatments into specific types was available from our previous NMA. An additional study[32] and additional eligible arms[33] from multi-arm studies not included in the NMA were extracted and included to reflect all eligible studies and available comparisons.

Coding of constituent components in all included arms of studies was conducted according to the definitions in **Table 1**, based on information from study manuscripts, appendices and, when applicable, from online resources for commercial intervention programs. Included components were chosen through consultation with clinicians and examination of the literature on cNMAs and CCT to establish the common 'active ingredients' of CCT and control treatments.[9,14,21,23,28,34]

Table 1. List of included components and their definitions

Component		Description
pc	Passive control	Wait-list or no-contact control group.
exb	Expectancy bias	Effect of an intervention or active control due to the patients' belief that they are receiving some form of treatment.
pe	Psychoeducation	Provision of information about the cause and nature of cognitive impairment and general cognitive stimulation.
su	Supervised delivery	Interventions provided mainly or exclusively outside of home (e.g., at a medical clinic, hospital, community centre, research clinic) in a supervised setting.
ic	Intermittent contact	Intermittent contact from research staff or clinicians whilst training from home, such as adherence to the intervention being monitored remotely and participants contacted for check-ins or to discuss less-than-expected training.
soc	Socialization	Facilitated interaction or discussion between participants, such as discussion groups or role-playing activities.
ad	Adaptive training	Training difficulty is adapted over time in response to participant performance. This may be either in a staircase design, where level or difficulty increases or decreases *within a block* in response to

		participant performance, or in a block design, where level increases or decreases at the end of a block of trials in response to performance. If training difficulty is increased over time *without regards* to participant performance, it is not considered adaptive.
st	Strategy training	Explicit teaching of cognitive strategies (e.g., mnemonic techniques for memory, or logic and planning techniques for reasoning).
ct	Classical cognitive training	Traditional computerised cognitive training interventions or programs, including both single domain and multidomain training.
md	Multidomain training	Training targeting several cognitive components (e.g., executive function and working memory) as opposed to single domain training (e.g., working memory).
ga	Gamification	Clear use of game elements in the intervention or program (e.g., avatars, stories and themes, sound effects, rewards such as badges and other digital rewards for accomplishing certain tasks, visual features that inform users of task-related progress through the game such as progress bars, digital social interaction with other users, competition against other users such as leader boards).
avg	Action video game	Video games that emphasise physical challenges, including hand-eye coordination and reaction time (e.g., Grand Theft Auto, Call of Duty, Medal of Honor, Unreal Tournament).
cg	Casual games	Casual non-action video games, strategy games and puzzles (e.g., SIMS, Tetris, Angry Birds, sudoku, crosswords).
ca	Casual activities	Casual activities (e.g., reading, watching movies, documentaries) as well as low-intensity educational activities (e.g., data entry, using Word or Excel software, learning to use internet search engines).
ex	Physical exercise	Prescribed physical exercise (including aerobic exercise and/or resistance training).

Data Synthesis

Analyses were conducted using the package netmeta[35] in R, version 4.0.2 (The R Foundation for Statistical Computing). The primary outcome was overall cognition, defined as a composite of all eligible outcomes reported in each study, reflecting global cognitive performance.[14,21] Between-group differences in change from baseline to post-intervention were converted to standardised mean differences and calculated as Hedges' *g* with 95% confidence interval (CI) for each eligible outcome measure. Pooling of outcomes within studies into the overall cognitive composite was conducted using Gleser & Olkin's method for handling stochastically dependent effect sizes,[36] with rho=0.5 to reduce overestimation of within-study variance due to multiple effect-sizes within studies.

Heterogeneity across studies was quantified using τ^2 and expressed as a proportion of overall observed variance using the I^2 statistic.[37,38] Both NMA and cNMA were performed using a frequentist framework in the netmeta package.

First, NMA using the main CCT and control types as nodes in reference to no contact (passive control) was performed to corroborate the findings of our previous NMA.[21] Network geometry of direct comparisons was summarised in a network graph and a league table was created to display the relative effect sizes of all available comparisons. Ranking of treatments was estimated using P-scores, representing the extent of certainty that a treatment is more effective than another.[39] Second, cNMA of CCT and control treatments as combinations of components was performed, once again in reference to no contact (passive control, *pc*). For the analysis, passive control was classified as an inactive component as it does not have any therapeutic value other than accounting for retest effect and non-specific factors related to study participation. Some examples of common CCT and control treatments included in the analysis at the component level are provided in **Table 2.**

Table 2. Conceptualisation of component composition of various CCT modalities and controls

Interventions or controls	Possible decompositions into components
No treatment/Waitlist	*pc*
Multidomain CCT	*exb (± pe ± su/ic ± soc ± ad ± st) + ct + md (± ga ± ex)*
Single domain CCT	*exb (± pe ± su/ic ± soc ± ad ± st) + ct (± ga ± ex)*
Sham CCT	*exb (± pe ± su/ic ± soc ± ad ± st ± ga ± ex)*
Action video games	*exb (± pe ± su/ic ± soc ± ad ± st ± ga) + avg (± ex)*
Psychoeducation	*exb + pe (± su/ic ± soc ± st ± ex)*
Strategy training	*exb (± pe ± su/ic ± soc) + st (± ex)*
Physical exercise	*exb (± pe ± su/ic ± soc ± st) + ex*
Casual games or puzzles	*exb (± pe ± su/ic ± soc ± st ± ga) + cg (± ex)*
Casual activities	*exb (± pe ± su/ic ± soc ± st ± ga) + ca (± ex)*

Abbreviations: *pc*, passive control; *exb*, expectancy bias; *pe*, psychoeducation; *su*, supervised delivery; *ic*, intermittent contact; *soc,* socialisation; *ad*, adaptive training; *st*, strategy training; *ct*, classical cognitive training; *md*, multidomain training; *ga*, gamification; *avg*, action video game; *cg,* casual games; *ca,* casual activities; *ex*, physical exercise. Note that components in parentheses are elective/optional. Symbols: '+' means 'and'; '±' means 'with or without'; '/' means 'or'.

Network geometry of direct treatment comparisons was summarised in a network graph. For the cNMA, we employed an additive model, whereby the overall effect of a treatment is assumed equal to the sum of the effects of its constituent components (positive or negative).[24] According to this model, comparing composite treatment *A*, containing components *x*+*y*, to treatment *C*, containing only component *x*, estimates the effect of component *y*. Similarly, comparing composite treatment *B*, containing components *x*+*y*+*z*, to treatment *C*, containing only component *x*, estimates the effect of components *y*+*z*. To examine the transitivity assumption, which is when it is equally likely that any participant in a network of treatment comparisons could have been given any other treatment in the network, a table summarising treatment components and potential effect modifiers (population and design characteristics) was created and visually inspected to explore whether these were similarly distributed. In addition, to assess network consistency, effect estimates for treatment comparisons were split into the contribution of direct and indirect evidence and differences visually inspected when direct evidence from ≥3 studies existed for a treatment comparison.

Results

Characteristics of Included Studies

Key study characteristics and the composition of treatment arms at the component level are reported in **Table S1 and S2 in the appendix**, respectively. The 91 included RCTs across 218 CCT and control arms encompassed 134 eligible pairwise comparisons and 9,269 unique participants.

Assessment of Transitivity Assumption

Treatment types, treatment components and population and design characteristics (mean age, percent female, baseline MMSE score, treatment dose and risk of bias) that are potential effect modifiers are summarised in **Table S2 in the appendix**. Visual inspection across treatment types and components showed that potential effect modifiers were similarly distributed across the network, leaving little concern about validity of the transitivity assumption.

Network Meta-Analysis

The included studies spanned 13 CCT and control treatment types and resulted in a well-connected network structure (**Figure 2**). Direct evidence was available for 35 comparisons, most notably multidomain vs. no contact (k=18), multidomain vs. CS/Education (k=18) and working memory training vs. sham CCT (k=14). Residual heterogeneity in the NMA was minimal (τ^2=0.004; I^2=9.2%).

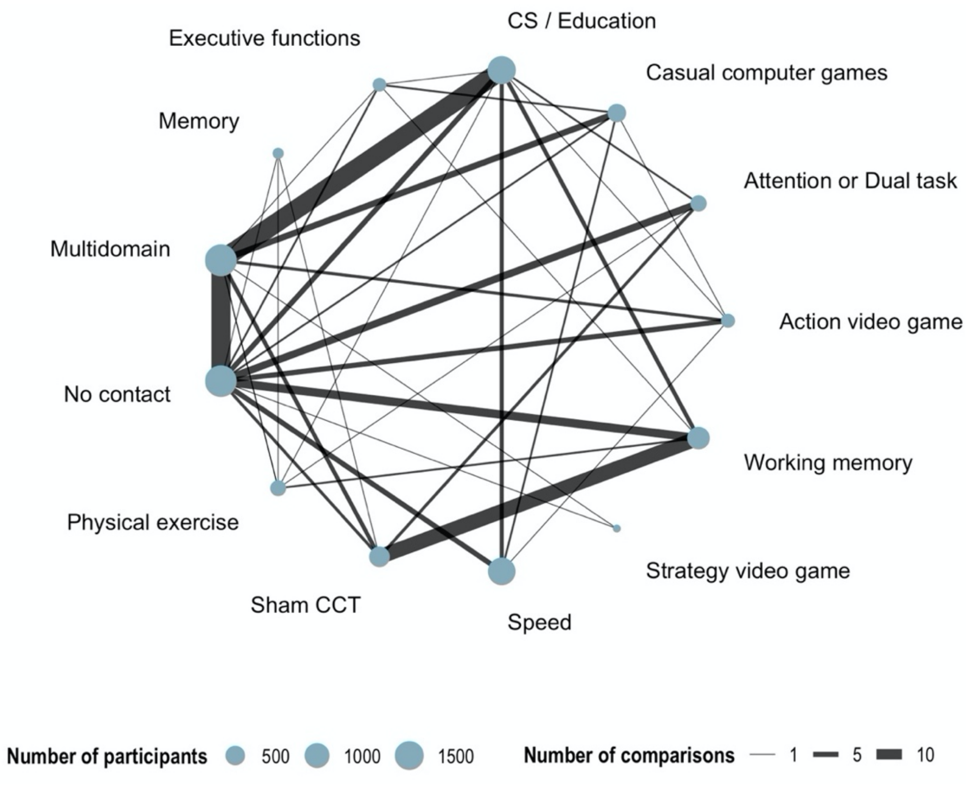

Figure 2. Network structure for CCT and control type treatments.

Treatment estimates are provided in **Figure 3**. Across all trials, speed training ranked highest for efficacy on overall cognition, with a small statistically significant effect size over and above no contact. Multidomain training ranked second highest and working memory training third highest, both also with small and statistically significant effect sizes over and above no contact. Additionally, speed training, multidomain training and working memory training all had small statistically significant effect estimates over and above all active control conditions asides from physical exercise (**Table S3 in the appendix**). However, there were no substantial differences between these three treatments in terms of effect size or P-score.

Treatment	***k***	**Hedges' *g* (95% CI)**	**P-score**
Speed	12	0.23 (0.12, 0.33)	0.79
Multidomain	53	0.21 (0.13, 0.30)	0.76
Working memory	29	0.20 (0.09, 0.32)	0.72
Action video game	11	0.20 (-0.01, 0.42)	0.69
Attention or Dual task	13	0.19 (0.05, 0.34)	0.69
Memory	3	0.19 (-0.08, 0.45)	0.64
Strategy video game	2	0.17 (-0.15, 0.49)	0.59
Executive functions	7	0.09 (-0.12, 0.29)	0.39
Physical exercise	7	0.09 (-0.08, 0.26)	0.37
Sham CCT	25	0.06 (-0.06, 0.18)	0.30
CS / Education	36	0.05 (-0.04, 0.15)	0.27
Casual computer games	13	0.02 (-0.13, 0.16)	0.18

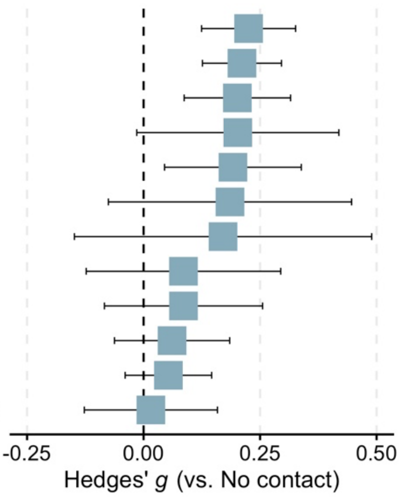

Figure 3. Treatment estimates for CCT and control type vs. no contact. Note: *k* is the number of studies that included each treatment type.

There was evidence of inconsistency for three comparisons, with the direct effect size estimate larger than the indirect estimate for multidomain vs. no contact and speed vs. casual computer games, whilst the direct estimate was smaller than the indirect estimate for speed vs. no contact (**Table S3 in the appendix**).

Component Network Meta-Analysis

Dismantling of the CCT and control treatments of included studies into components led to 48 unique treatments at the component level and resulted in a well-connected network (**Figure 4**). Direct evidence was available for 62 treatment comparisons, most notably '*exb+su+ad+ct*' vs. '*pc*' (supervised adaptive single domain training vs. passive control; *k*=11), '*exb+su+ad+ct+md*' vs. '*pc*' (supervised adaptive multidomain training vs. passive control; *k*=7) and '*exb+ic+ad+ct*' vs. '*exb+ic*' (home-based adaptive single domain training with intermittent contact vs. home-based sham CCT with intermittent contact; *k*=6). Residual heterogeneity in the additive cNMA model (i.e., heterogeneity not captured by the model) was negligible (τ^2=0.001; I^2=2.5%).

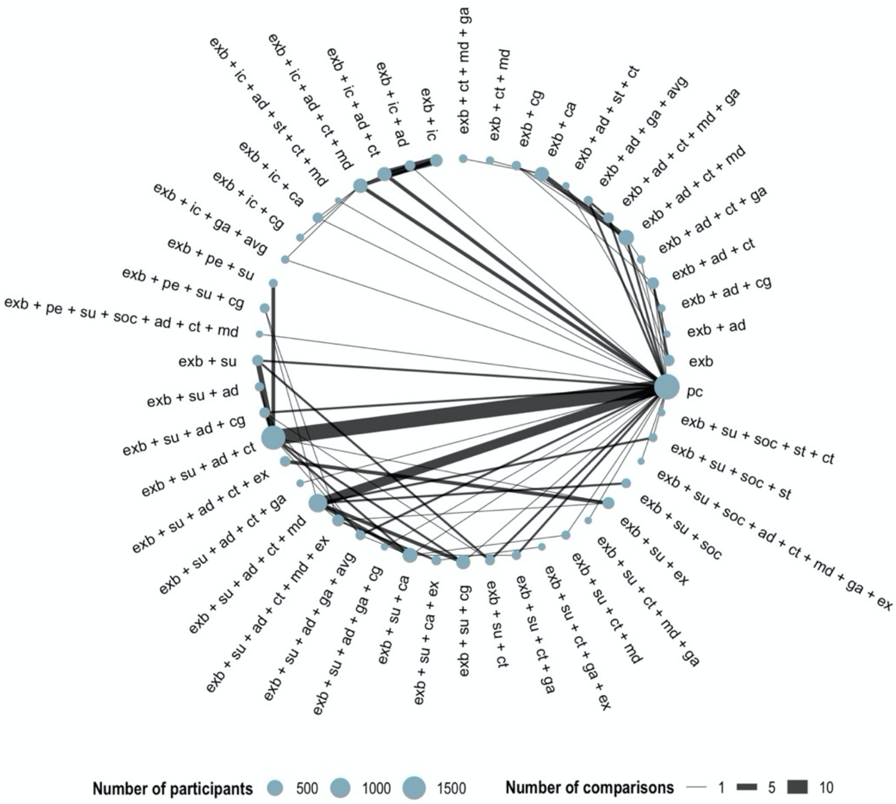

Figure 4. Network structure for treatments at component level. Abbreviations: *pc*, passive control; *exb*, expectancy bias; *pe*, psychoeducation; *su*, supervised delivery; *ic*, intermittent contact; *soc,* socialisation; *ad*, adaptive training; *st*, strategy training; *ct*, classical cognitive training; *md*, multidomain training; *ga*, gamification; *avg*, action video game; *cg,* casual games; *ca,* casual activities; *ex*, physical exercise. Symbols: '+' means 'and'.

Treatment and individual component estimates are provided in **Figures 5 and 6**. The treatments '*exb+ad+st+ct*' (home-based adaptive single domain training with strategy training), '*exb+su+soc+st+ct*' (supervised single domain training with strategy training and socialisation), '*exb+su+soc+st*' (supervised strategy training with socialisation), '*exb+pe+su+soc+ad+ct+md*' (supervised adaptive multidomain training with psychoeducation and socialisation) and '*exb+ic+ad+st+ct+md*' (home-based adaptive multidomain training with strategy training and intermittent contact) all had moderate and statistically significant effect size estimates over and above passive control. The treatments '*exb+ad+ct+md*' (home-based adaptive multidomain training), '*exb+su+ad+ct+md*' (supervised adaptive multidomain training), '*exb+ad+ct*' (home-based adaptive single domain training), '*exb+su+ad+ct*' (supervised adaptive single domain training), '*exb+su+ct+md*' (supervised multidomain training) and '*exb+su+ct*' (supervised single domain training) all had small and statistically significant effect size estimates over and above passive control. The component classical cognitive training had a small and statistically significant effect size over and above passive control. The components adaptive training, action video games, casual activities, expectancy bias, multidomain, psychoeducation, socialisation and strategy training all had positive, but non-significant, effect size estimates over and above passive control. Whilst, casual games, physical exercise, gamification, intermittent contact and supervised delivery all had negative, but non-significant, effect size estimates.

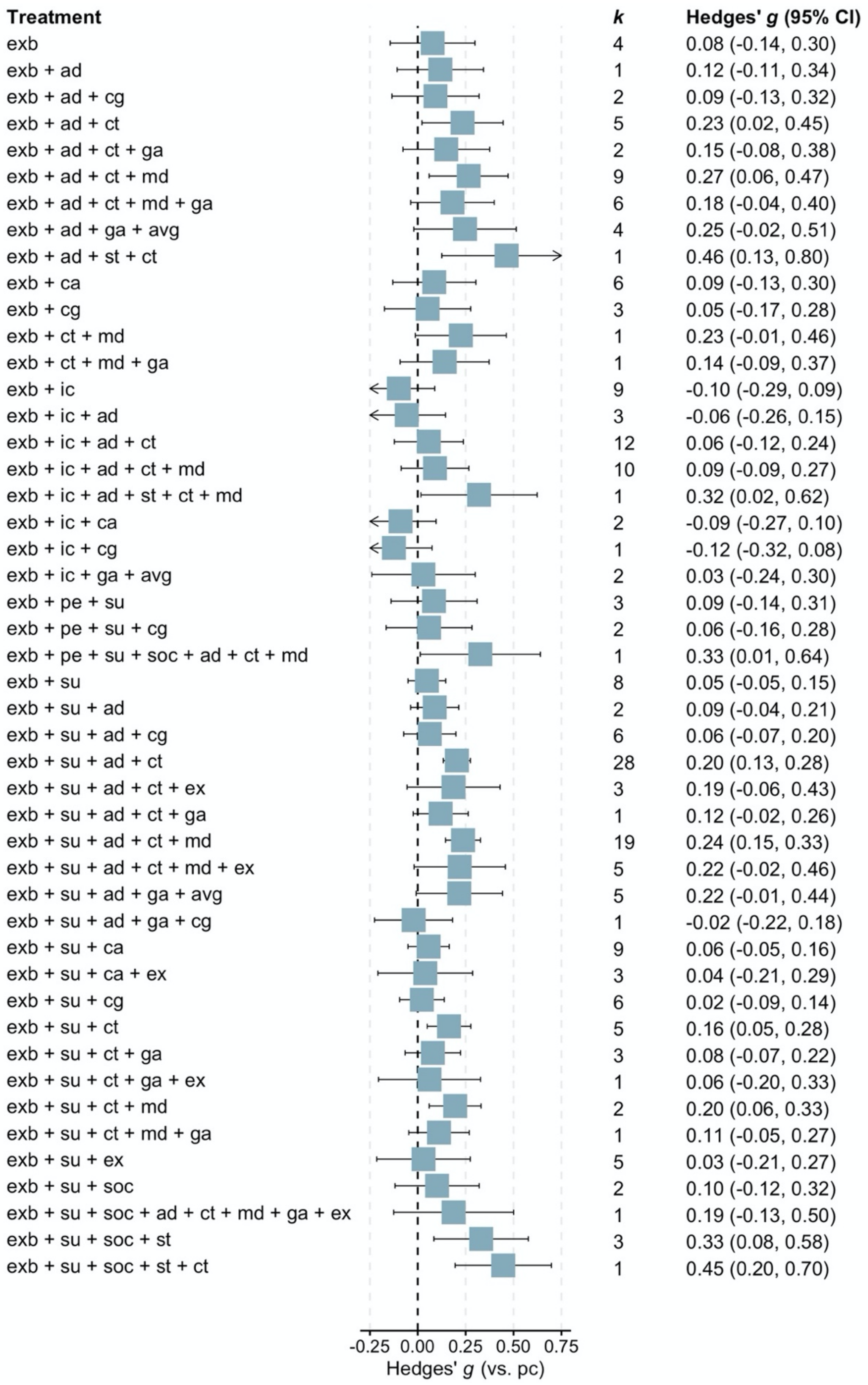

Figure 5. Treatment estimates at the component level for treatment vs. passive control. Abbreviations: *pc*, passive control; *exb*, expectancy bias; *pe*, psychoeducation; *su*, supervised delivery; *ic*, intermittent contact; *soc,* socialisation; *ad*, adaptive training; *st*, strategy training; *ct*, classical cognitive training; *md*, multidomain training; *ga*, gamification; *avg*, action video game; *cg,* casual games; *ca,* casual activities; *ex*, physical exercise. Symbols: '+' means 'and'. Note: *k* is the number of studies that included each treatment at the component level.

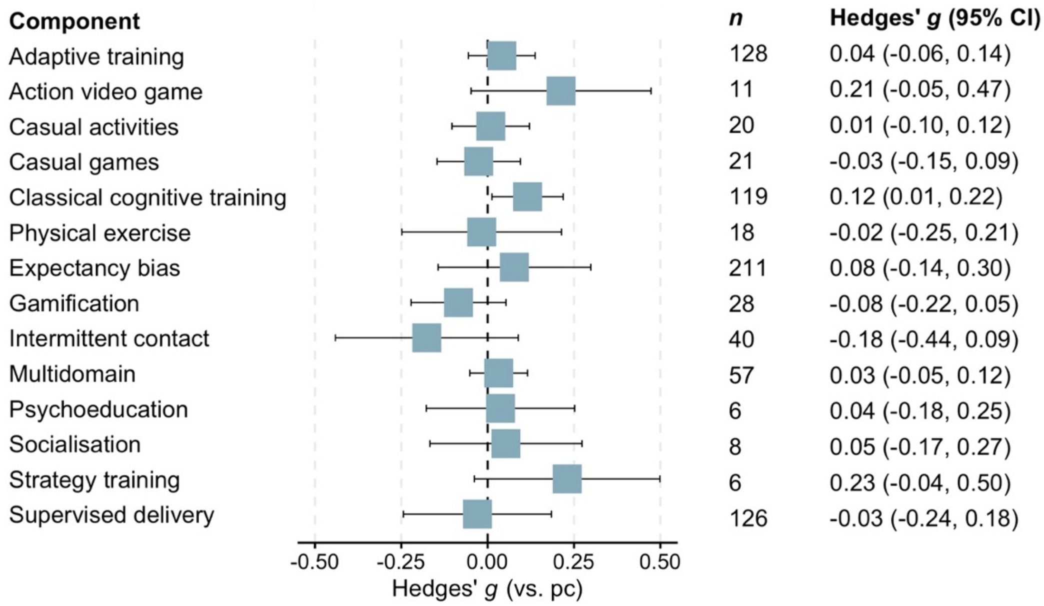

Figure 6. Treatment estimates of individual components vs. passive control. Note: *n* is the number of treatment arms that included each component.

There was evidence of inconsistency between direct and indirect effect size estimates for five treatment comparisons (**Table S4 in the appendix**). Direct evidence underestimated the efficacy of the treatment comparisons ‘*exb+ic+ad+ct+md*’ vs. ‘*pc*’ (home-based adaptive multidomain training with intermittent contact vs. passive control), ‘*exb+su*’ vs. ‘*exb+su+ad+ct*’ (supervised sham CCT vs. supervised adaptive single domain training), ‘*exb+su+ad+ct*’ vs. ‘*pc*’ (supervised adaptive single domain training vs. passive control) and ‘*exb+su+ad+ct+md*’ vs. ‘*exb+su+cg*’ (supervised adaptive multidomain training vs. supervised casual games) compared to the indirect evidence. Whilst direct evidence overestimated the efficacy of the treatment comparison ‘*exb+su+ad+ct+md*’ vs. ‘*pc*’ (supervised adaptive multidomain training vs. passive control) compared to the indirect evidence.

Discussion

Understanding the 'active ingredients' underlying the cognitive benefits of CCT is critical for future intervention design and clinical rollout.[14,21] Across 218 intervention and control arms encompassing 134 pairwise comparisons, this cNMA of 91 RCTs of CCT in healthy older adults has narrowed down the components and modalities (i.e., combinations of components) which are associated with more robust cognitive gains. In particular, structured approaches to cognitive training are beneficial, especially when exercises are adaptive, and their efficacy can be further enhanced when participants are also taught classical cognitive strategies such mnemonics and chunking. Moreover, intervention components that aim to make training more engaging, most notably action video games and socialisation, are associated with greater gains. It should be noted, however, that relatively few studies used these components and therefore estimates of their added benefit over and above standard cognitive training are still imprecise.

Engaging in non-structured cognitively stimulating activities has been associated with better cognitive performance in observational studies[5-7] and is commonly recommended as a viable alternative to cognitive training.[16,40] However, our results do not support this approach, with the cognitive benefits of such activities (e.g., reading, crossword puzzles) substantially smaller than those of CCT and unlikely to be more beneficial than passive control. Since such activities do not lead to benefits beyond those associated with trial participation (e.g., repeated testing), they have limited value as 'active control' conditions. As such, future head-to-head trials comparing two potentially efficacious training approaches or components may be prioritised over comparison to inert or passive control. Moreover, previous claims touting CCT as an "opportunity cost" to engage in other activities such as gardening or playing with grandchildren[40] do not seem to be supported by the evidence and should be reconsidered.

Whilst our findings support theoretical predictions regarding the potential of implicit learning and motivational cues to enhance CCT effects,[10] estimates of several individual components revealed surprising results. In particular, negative (albeit imprecise) effect estimates were found for supervised delivery and intermittent contact, which were expected to have positive effect estimates given supervised delivery has been found to be more efficacious than home-based delivery in previous reviews of CCT in healthy older adults.[14,21] This may be due to limitations in model specification or that there are synergistic or antagonistic interactions between some components, which are unable to be accounted for by the additive model we have employed. For example, supervision by itself is a non-specific intervention factor that may not have cognitive benefit as a standalone component, but its interaction with specific factors (i.e., cognitive training) may augment the effect. Although methods for modelling such interactions are in their infancy,[41] further work will be able to better model the complex interplay between components and how these can be combined to deliver more efficacious interventions.

To the best of our knowledge, this is the first cNMA of CCT in healthy older adults, addressing not only the question "*Are CCT treatments in general efficacious?*" but more so "*Which CCT treatment modalities and components are most efficacious?*". Nonetheless, some limitations should be addressed. First, as we employed a frequentist framework we were limited to an additive model. A future step would be to switch to a Bayesian framework to allow for the inclusion of potential effect moderators in the cNMA model.[41] Second, as cognitive domains of training were not included as components, the foci of single domain training regimens could not to be differentiated. An extension of this analysis could include the cognitive domains targeted by the different programs as additional components, although the feasibility of adding additional content components needs to be investigated. Third, the definitions and identification of components within CCT treatments and controls adhere to theoretical accounts of CCT effects[9,10,14,21,23,28,34,42] but are inherently arbitrary, especially when individual studies provide only partial information regarding the intervention approach.

Overall, in this review we have found that CCT is efficacious for overall cognition for healthy older adults, with adaptive CCT combined with strategy training showing promise as a potentially more efficacious treatment than CCT alone. A next step would be to conduct a component individual participant data meta-analysis to examine interactions between components as well as participant level characteristics to determine which modalities are most efficacious in different patient subgroups. This information will be critical to ensure that future treatments are able to be personalised to achieve optimal clinical benefit.

References

1. Patterson C. *World Alzheimer Report 2018.* London: Alzheimer’s Disease International;2018.
2. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet.* 2020;396(10248):413-446.
3. Yu JT, Xu W, Tan CC, et al. Evidence-based prevention of Alzheimer's disease: systematic review and meta-analysis of 243 observational prospective studies and 153 randomised controlled trials. *J Neurol Neurosurg Psychiatry.* 2020;91(11):1201-1209.
4. Marioni RE, Valenzuela MJ, van den Hout A, et al. Active cognitive lifestyle is associated with positive cognitive health transitions and compression of morbidity from age sixty-five. *PLoS One.* 2012;7(12):e50940.
5. Verghese J, Lipton RB, Katz MJ, et al. Leisure activities and the risk of dementia in the elderly. *N Engl J Med.* 2003;348(25):2508-2516.
6. Wilson RS, Mendes De Leon CF, Barnes LL, et al. Participation in cognitively stimulating activities and risk of incident Alzheimer disease. *JAMA.* 2002;287(6):742-748.
7. Lee ATC, Richards M, Chan WC, Chiu HFK, Lee RSY, Lam LCW. Association of Daily Intellectual Activities With Lower Risk of Incident Dementia Among Older Chinese Adults. *JAMA Psychiatry.* 2018;75(7):697-703.
8. Douglas KM, Milanovic M, Porter RJ, Bowie CR. Clinical and methodological considerations for psychological treatment of cognitive impairment in major depressive disorder. *BJPsych Open.* 2020;6(4):e67.
9. Keshavan MS, Vinogradov S, Rumsey J, Sherrill J, Wagner A. Cognitive training in mental disorders: update and future directions. *Am J Psychiatry.* 2014;171(5):510-522.
10. Sikkes SAM, Tang Y, Jutten RJ, et al. Toward a theory-based specification of non-pharmacological treatments in aging and dementia: Focused reviews and methodological recommendations. *Alzheimers Dement.* 2020.
11. *Preventing Cognitive Decline and Dementia: A Way Forward.* Washington (DC)2017. Downey A, Stroud C, Landis S, Leshner AI, eds.
12. Gavelin HM, Lampit A, Hallock H, Sabates J, Bahar-Fuchs A. Cognition-Oriented Treatments for Older Adults: a Systematic Overview of Systematic Reviews. *Neuropsychol Rev.* 2020;30(2):167-193.
13. Basak C, Qin S, O'Connell MA. Differential effects of cognitive training modules in healthy aging and mild cognitive impairment: A comprehensive meta-analysis of randomized controlled trials. *Psychol Aging.* 2020;35(2):220-249.
14. Lampit A, Hallock H, Valenzuela M. Computerized cognitive training in cognitively healthy older adults: a systematic review and meta-analysis of effect modifiers. *PLoS Med.* 2014;11(11):e1001756.
15. Gavelin HM, Dong C, Minkov R, et al. Combined physical and cognitive training for older adults with and without cognitive impairment: A systematic review and network meta-analysis of randomized controlled trials. *Ageing Res Rev.* 2021;66:101232.
16. Simons DJ, Boot WR, Charness N, et al. Do "Brain-Training" Programs Work? *Psychol Sci Public Interest.* 2016;17(3):103-186.

17. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med.* 2004;23(20):3105-3124.
18. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ.* 2005;331(7521):897-900.
19. Cipriani A, Higgins JP, Geddes JR, Salanti G. Conceptual and technical challenges in network meta-analysis. *Ann Intern Med.* 2013;159(2):130-137.
20. Efthimiou O, Debray TP, van Valkenhoef G, et al. GetReal in network meta-analysis: a review of the methodology. *Res Synth Methods.* 2016;7(3):236-263.
21. Lampit A, Malmberg Gavelin H, Sabates J, et al. Computerized Cognitive Training in Cognitively Healthy Older Adults: A Systematic Review and Network Meta-Analysis. *medRxiv.* 2020:2020.2010.2007.20208306.
22. Welton NJ, Caldwell DM, Adamopoulos E, Vedhara K. Mixed treatment comparison meta-analysis of complex interventions: psychological interventions in coronary heart disease. *Am J Epidemiol.* 2009;169(9):1158-1165.
23. Pompoli A, Furukawa TA, Efthimiou O, Imai H, Tajika A, Salanti G. Dismantling cognitive-behaviour therapy for panic disorder: a systematic review and component network meta-analysis. *Psychol Med.* 2018;48(12):1945-1953.
24. Rucker G, Petropoulou M, Schwarzer G. Network meta-analysis of multicomponent interventions. *Biom J.* 2020;62(3):808-821.
25. Lopez-Lopez JA, Davies SR, Caldwell DM, et al. The process and delivery of CBT for depression in adults: a systematic review and network meta-analysis. *Psychol Med.* 2019;49(12):1937-1947.
26. Furukawa TA, Karyotaki E, Suganuma A, et al. Dismantling, personalising and optimising internet cognitive-behavioural therapy for depression: a study protocol for individual participant data component network meta-analysis. *BMJ Open.* 2019;8(11):e026137.
27. Freeman SC, Scott NW, Powell R, Johnston M, Sutton AJ, Cooper NJ. Component network meta-analysis identifies the most effective components of psychological preparation for adults undergoing surgery under general anesthesia. *J Clin Epidemiol.* 2018;98:105-116.
28. Melendez-Torres GJ, Bonell C, Thomas J. Emergent approaches to the meta-analysis of multiple heterogeneous complex interventions. *BMC Med Res Methodol.* 2015;15:47.
29. Costantini I, Paul E, Caldwell DM, Lopez-Lopez JA, Pearson RM. Protocol for a systematic review and network meta-analysis of randomised controlled trials examining the effectiveness of early parenting interventions in preventing internalising problems in children and adolescents. *Syst Rev.* 2020;9(1):244.
30. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ.* 2009;339:b2700.
31. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med.* 2015;162(11):777-784.
32. Buschkuehl M, Jaeggi SM, Hutchison S, et al. Impact of working memory training on memory performance in old-old adults. *Psychol Aging.* 2008;23(4):743-753.
33. Ten Brinke LF, Best JR, Chan JLC, et al. The Effects of Computerized Cognitive Training With and Without Physical Exercise on Cognitive Function in Older Adults:

An 8-Week Randomized Controlled Trial. *J Gerontol A Biol Sci Med Sci.* 2020;75(4):755-763.
34. Lumsden J, Edwards EA, Lawrence NS, Coyle D, Munafo MR. Gamification of Cognitive Assessment and Cognitive Training: A Systematic Review of Applications and Efficacy. *JMIR Serious Games.* 2016;4(2):e11.
35. Rücker G, Krahn U, König J, Efthimiou O, Schwarzer G. netmeta: Network meta-analysis using frequentist methods. *R package Version 12-1.* 2020.
36. Gleser LJ, Olkin I. Stochastically dependent effect sizes. In: Cooper H, Hedges L, Valentine J, eds. *The handbook of research synthesis and meta-analysis, 2nd Edition.* New York: Russell Sage Foundation; 2009:357-376.
37. Borenstein M, Higgins JP, Hedges LV, Rothstein HR. Basics of meta-analysis: I(2) is not an absolute measure of heterogeneity. *Res Synth Methods.* 2017;8(1):5-18.
38. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med.* 2002;21(11):1539-1558.
39. Rucker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Med Res Methodol.* 2015;15:58.
40. Stanford Center on Longevity. A Consensus on the Brain Training Industry from the Scientific Community. http://longevity3.stanford.edu/blog/2014/10/15/the-consensus-on-the-brain-training-industry-from-the-scientific-community-2/. Published 2014. Accessed 17 December, 2020.
41. Petropoulou M, Efthimiou O, Rucker G, et al. A review of methods for addressing components of interventions in meta-analysis. *PLoS One.* 2021;16(2):e0246631.
42. Lustig C, Shah P, Seidler R, Reuter-Lorenz PA. Aging, training, and the brain: a review and future directions. *Neuropsychol Rev.* 2009;19(4):504-522.